

## **REMARKS**

Receipt is acknowledged of the Office Action mailed April 20, 2004. Applicants respectfully request reconsideration in view of the foregoing amendments and the following commentary.

In the specification, lines have been amended on pages 1, 2, and 12. Claims 1-13 are currently being amended. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. After amending the claims as set forth above, claims 1-13 are still pending in this application and presented for consideration.

### **Objection to the Title**

The Examiner objected to the use of "GnRH-II" in the title. In response and as recommended by the Examiner, applicants amended the title to recite "Controlled Release Formulation Comprising Gonadotropin Releasing Hormone-II" to overcome the objection.

### **Objection to the Specification**

The Examiner objected to the use of "(7)" after the sequence. Accordingly, applicants amended the specification to replace "(7)" with "SEQ ID NO: 7" to overcome the objection. In addition, applicants have replaced "(6)" with "SEQ ID NO: 6" throughout the specification. Further, applicants corrected the misspelling of the term "osteoclastic" pointed out by the Examiner.

### **Objection to Improper Multiple Dependent Claims**

The Examiner objected to claim 6 because it was an improper dependent claim. In response, applicants amended claim 6 to depend from claim 1. Applicants believe that this amendment will overcome the objection.

**Statement of Statutory Basis**

The Examiner objected to claims 8-10 because they recited a use without setting forth the steps involved in the process. Applicants have amended claim 8 to recite “a method for preparing a controlled release medicament” and have set forth the steps involved in the preparation. Applicants believe that this amendment will overcome the objection.

**35 U.S.C. § 112, ¶ 2 - The Claims are Definite**

The Examiner rejected claim 1 as indefinite because he alleged that it was unclear whether the peptide was SEQ ID NO: 7 and what “a salt thereof” referred to. In response, applicants amended claim 1 to make clear that the claim recites a pharmaceutical formulation and that the peptide comprises SEQ ID NO: 7 as illustrated or a salt thereof. Applicants believe that the claim is, and was, clear.

The Examiner also rejected claim 3 because he found it unclear what kind of copolymer the claim recited. Applicants have amended the claim to recite that the polymer comprises a polymer of a hydroxyl derivative of a carboxylic acid, a polymer of an amino derivative of a carboxylic acid, or a copolymer of the carboxylic acid derivatives. Applicants believe that this amendment clarifies the language of the claim. Support for this amendment can be found on page 3, second paragraph.

Further, the Examiner rejected claim 6 as indefinite because he alleges that the treatment of a medical condition is not defined in the specification. Applicants amended the claim to recite the treatment of a human pathology. Support for this amendment is found on page 3, last paragraph, and page 4, first paragraph. The specification describes human pathologies such that one of skill in the art would understand the metes and bounds of the claim.

The Examiner also rejected claims 8-10 for lacking process steps. As mentioned above, applicants have amended claim 8 to recite “a method for preparing a controlled release

medicament” and have set forth the steps involved in the preparation. Applicants believe that this amendment will overcome the rejection.

Finally, the Examiner rejected claims 10, 11, and 13 as indefinite for the recitation of “various disorders.” Applicants have amended the claims to place them in proper Markush format and believe that the amendment will overcome the rejection.

**35 U.S.C. § 112, ¶ 1 - The Claims are Enabled**

The Examiner also rejected claims 6-13 under 35 U.S.C. § 112, ¶ 1 for lack of enablement. Applicants gratefully acknowledge that the Examiner agrees that the pharmaceutical formulations of claims 1-5 are enabled and wish to explain why a skilled artisan would be able to make and use the pharmaceutical formulations and methods according to claims 6-13 without undue experimentation.

As an initial matter, without acquiescing in the rejection and without intending to abandon claimed subject matter but to expedite allowance, claims 7, 8, and 10-13 have been amended to remove the recitation of “prostate growth” and/or “benign prostatic hyperplasia and prostate cancer.” Applicants reserve the right to file a continuing application directed to this subject matter.

Accordingly, present claims 7-13 are drawn to pharmaceutical formulations for treating or protecting against disorders of bone growth, to a methodology for preparing a controlled release medicament for these purposes, and to a methodology for treating bone-growth disorders. Applicants submit that the pharmaceutical formulations, the methods of preparing a controlled release medicament, and the methods of treatment are all fully and clearly enabled by the present specification.

The Examiner acknowledges that one of skill in the art would know how to make and use the pharmaceutical formulation recited in claim 1. Moreover, the Examiner acknowledges that the methods for preparing a controlled release medicament recited in claims 8-10 are described

on pages 4-9, Examples 1 and 2, and Tables 1 and 2. In particular, the specification describes how to provide a peptide according to SEQ ID NO: 7 by solid-phase synthesis and by solution-phase synthesis. *See* pages 4-5. In addition, the specification describes two ways to incorporate the peptide into a pharmaceutically acceptable biodegradable polymer, *i.e.*, by simple dispersion and by encapsulation. *See* page 6-7 and Example 2. With this knowledge, one skilled in the art could make a controlled release medicament according to the claimed method without undue experimentation. In addition, given that the pharmaceutical formulation recited in claim 1 is enabled, one skilled in the art would be able to administer that formulation to a patient in accordance with claims 6, 12, and 13.

The Examiner, however, questions whether one skilled in the art would know what dosages to administer to effectively treat, or protect against, a human pathology, such as a disorder of bone growth. The Examiner asserts that “one cannot administer [a] specific effective amount of a pharmaceutical formulation in all situation[s] without appropriate testing.” In other words, the Examiner claims that one skilled in the art would not know how much of the pharmaceutical formulation to administer to ensure that it is “a therapeutically effective amount” as recited in claim 6.

That some experimentation may be required to identify optimal dosages, however, does not mean that the experimentation necessarily is “undue.” It is well established that the relevant prohibition is against “undue experimentation” and not merely “experimentation” *per se*. *In re Angstadt*, 537 F.2d 498, 502- 03 (CCPA 1976). In fact, selecting dosages is exactly the type of thing that is known in the art. We only have to look to everyday occurrences to realize that, as a practical matter, those skilled in the art have been identifying appropriate dosages for numerous drugs already on the market. Although there is some experimentation involved in selecting the appropriate dosage, it is well within the skill in the art and such experimentation is not undue.

To show how the current specification contributes to the dosing strategy for the claimed peptides, such that any experimentation that may be required is not undue, applicants wish to

direct the Examiner's attention to page 2, lines 1-2 and page 4, lines 12-20. Here, applicants make clear that intramuscular and subcutaneous injection of the claimed formulation(s) at doses of, for example, between 1 mg and 1 g, provides controlled release of the peptide to the systemic circulation sufficient to treat disorders of bone growth. Further, Examples 3, 4, and 6 illustrate that the level of systemic circulation required for therapeutic activity can be less than 100  $\mu$ M. Dosage strategies are well-known in the medical art and those skilled in the art are aware that the dosage of a drug can vary between patients. The preferred dosage, therefore, will depend upon the disorder being treated, the therapeutic compound, and the patient, among other factors. Those skilled in the art know how to select the appropriate dosages for a specific subject and situation and can do so without undue experimentation.

The Examiner further questions whether the recited peptides are expected to be useful for the kinds of human pathologies that are disclosed and claimed in claims 6-13. Applicants submit that the experiments described in the Examples clearly illustrate that the peptides are effective against the human pathologies that are disclosed and claimed in claims 6-13. The specification shows the expression analysis of GnRH-II and analogues thereof in Osteogenic cell populations and Osteoclast propulations *in vitro*. See Examples 3-5. Further, it describes the cellular localization of GnRH-II in sections of normal rat bone and human bone. See Example 7. In addition, the specification describes the effects of increasing doses of GnRH-II on serum calcium levels *in vivo* in ovariectomized Sprague Dawley rats. See Example 6. Sprague Dawley rats, such as those used in these experiments, are widely accepted, dependable, general purpose research model used in virtually all disciplines of biomedical research including toxicology and pharmacology and have even been employed by NIH Animal Genetic Resource. See [www.taconic.com/anmodels/spragued.htm](http://www.taconic.com/anmodels/spragued.htm) (copy enclosed).

With respect to the role of GnRH-II on calcium homeostasis, illustrated in Example 6, applicants concluded that, in the absence of fluctuations in the control group, the short-term changes in calcium are attributable to the administration of parathyroid hormone ("PTH") and GnRH-II peptides. See Figure 1. Plasma calcium is maintained within a very narrow range by a

complex interplay of several known hormones, including PTH, 1,25-dihydroxyvitamin D (*i.e.*, calcitriol), and calcitonin. These hormones act primarily at bone, kidney, and small intestine sites to maintain appropriate calcium levels. For hypocalcaemia to develop, the normal calcium regulation system must be overwhelmed by an excess of blood levels of PTH, calcitriol, or some other serum factor that can mimic these hormones. The localization of GnRH-II peptide in key cells in bone sections, as shown by immunochemistry, is strong evidence for the site of action being within the bone itself. This fact, coupled with the effects of GnRH-II on bone cells *in vitro*, illustrated in Examples 3 and 4, substantiates a role for GnRH-II in bone metabolism. Further, applicants' statement in Examples 3 and 4, that "the peptides of the invention caused significant effects at concentrations below 100  $\mu$ M," reasonably conveys their demonstration of the osteogenic effects of GnRH-II at low dosages, between  $10^{-9}$  and  $10^{-6}$ M, which is contrary to what one might expect from high molar effects described in other papers.

These experiments show that the pharmaceutical formulation recited in claim 1 and the controlled release medicament made by the methods recited in claims 8-10 increase bone mineral density *in vivo* (Example 7). Accordingly, one skilled in the art would know that the formulation and medicament can be used to treat, or protect against, a disorder of bone growth as recited in claims 7 and 8. In addition, those skilled in the art, knowing that GnRH-II treats and protects against disorders of bone growth, would be able to select the appropriate dosage to ensure that the pharmaceutical formulation is therapeutically effective.

Finally, we turn to dependent claims 10-11 and 13, which recite the use of the claimed pharmaceutical formulation or controlled release medicament to treat any of the following disorders: age-related osteoporosis, osteoporosis associated with post-menopausal hormone status, primary and secondary hyperparathyroidism, disuse osteoporosis, diabetes-related osteoporosis, and glucocorticoid-related osteoporosis. Applicants submit that these disorders are well known and understood. Osteoporosis, for example, is a well-known disorder of bone growth that affects 20 million Americans, about 80% of them women, and is described as "an age-related disorder characterized by decreased bone mass and increased susceptibility to

fractures.” STEDMAN'S ONLINE MEDICAL DICTIONARY, 27th Edition (copy enclosed). Hyperparathyroidism also is a well-known condition that is “due to an increase in the secretion of the parathyroids, causing elevated serum calcium, decreased serum phosphorus, and increased excretion of both calcium and phosphorus, calcium stones and sometimes generalized osteitis fibrosa cystica.” *Id.* The showing in Figure 1 that GnRH-II significantly increases serum levels of calcium *in vivo* is sufficient to convince one skilled in the art that the recited formulation and medicament treat, or protect against, age-related osteoporosis, osteoporosis associated with post-menopausal hormone status, primary and secondary hyperparathyroidism, disuse osteoporosis, diabetes-related osteoporosis, and glucocorticoid-related osteoporosis as recited in claims 10-11 and 13.

Armed with the pharmaceutical formulation recited in claim 1, the steps of the methods recited in claims 6 and 8, the dosages for effective therapy or protection, and the knowledge that the peptides recited in the claims treat and protect patients from disorders of bone growth, one skilled in the art could make and use the claimed pharmaceutical formulations and methods without undue experimentation. Accordingly, applicants submit that claims 6-13 are enabled.

### **35 U.S.C. § 102(b) - The Claims are Novel**

A determination that a patent is invalid as being anticipated under 35 U.S.C. § 102 requires a finding that “each and every limitation is found either expressly or inherently in a single prior art reference.” *Celeritas Techs. Inc. v. Rockwell Int’l Corp.*, 150 F.3d 1354, 1360 (Fed. Cir. 1998). In addition, a reference must be enabling in order to anticipate a claim. *Akzo N.V. v. United States Int’l Trade Comm’n*, 1 USPQ2d 1241 (Fed. Cir. 1986).

### **Miyamoto Does Not Disclose All of the Elements in the Claims**

The Examiner rejected claims 1-3, 7, and 11 as allegedly anticipated by United States Patent No. 4,540,513 (“Miyamoto”). Specifically, the Examiner asserts that Miyamoto discloses a decapeptide having the formula pGlu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly-NH<sub>2</sub>. Applicants

submit that Miyamoto does not disclose the combination of the defined peptide and a “pharmaceutically acceptable biodegradable polymer” as recited by claim 1.

The Examiner tries to show that “acetic acid” is a pharmaceutically acceptable biodegradable polymer that is a hydroxyl derivative of carboxylic acid. Applicants would like to point out that acetic acid is not a polymer. Rather, it is a simple molecule that is not used as a polymer in Miyamoto. The peptide and acetic acid mixture could not be used as a controlled release formulation, because it has no pharmaceutically acceptable biodegradable polymer. Accordingly, Miyamoto does not disclose or suggest the pharmaceutical formulation set forth in claim 1. Since claims 2-3, 7, and 11 depend from claim 1, for at least this reason, these claims are patentable over Miyamoto.

Further, with respect to claim 3, applicants wish to point out that the claim recites “a polymer of a hydroxyl derivative of a carboxylic acid.” Acetic acid, which is a simple hydroxyl derivative of a carboxylic acid, is not sufficient to teach or suggest “a polymer of a hydroxyl derivative of a carboxylic acid” as recited by claim 3. For this additional reason, Miyamoto does not disclose or suggest the pharmaceutical formulation set forth in claim 3.

#### **Folkers Does Not Disclose All of the Elements in the Claims**

The Examiner also rejects claims 1-3, 7, and 11 as allegedly anticipated by United States Patent No. 4,721,775 (“Folkers”). The Examiner asserts that Folkers discloses five variations of decapeptides, which are identical to SEQ ID NO: 7. As with Miyamoto, applicants submit that Folkers does not disclose the combination of the defined peptide and a “pharmaceutically acceptable biodegradable polymer” as recited by claim 1.

The Examiner again asserts that “acetic acid” is a pharmaceutically acceptable biodegradable polymer that is a hydroxyl derivative of carboxylic acid. Applicants would like to point out that acetic acid is not a polymer. Rather, it is a simple molecule that is not used as a polymer in Folkers. The peptide and acetic acid mixture could not be used as a controlled release

formulation, because it has no pharmaceutically acceptable biodegradable polymer. Accordingly, Folkers does not disclose or suggest the pharmaceutical formulation set forth in claim 1. Since claims 2-3, 7, and 11 depend from claim 1, for at least this reason, these claims are patentable over Folkers.

Further, with respect to claim 3, applicants wish to point out that the claim recites “a polymer of a hydroxyl derivative of a carboxylic acid.” Acetic acid, which is a simple hydroxyl derivative of a carboxylic acid is not sufficient to teach or suggest “a polymer of a hydroxyl derivative of a carboxylic acid” as recited by claim 3. For this additional reason, Folkers does not disclose or suggest the pharmaceutical formulation set forth in claim 3.

#### **Tice Does Not Disclose All of the Elements in the Claims**

Finally, the Examiner rejects claims 1-5, 7, and 11 as allegedly anticipated by United States Patent No. 4,835,139 (“Tice”). Specifically, the Examiner asserts that Tice discloses pyro Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH<sub>2</sub> and that this is identical to SEQ ID NO: 7. Applicants wish to point out that the decapeptide disclosed in Tice is expressly excluded by the proviso in claim 1, which states that, for the peptide of SEQ ID NO: 7, “when Xaa<sup>1</sup> is Tyr and Xaa<sup>2</sup> is Leu, then Xaa<sup>3</sup> is not Arg.” Further, the other decapeptides disclosed in Tice do not fall within the applicants’ claimed limitation.

Accordingly, Tice does not disclose or suggest the pharmaceutical formulation set forth in claim 1. Since claims 2-5, 7, and 11 depend from claim 1, for at least this reason, these claims are patentable over Tice.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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**osteoporosis** (os'tē-ō-pō-rō'sis)

Reduction in the quantity of bone or atrophy of skeletal tissue; an age-related disorder characterized by decreased bone mass and increased susceptibility to fractures.

[osteo- + G. *poros*, pore, + -osis, condition]

Osteoporosis affects 20 million Americans, about 80% of them women, and costs U.S. society as much as \$3.8 billion annually. About 1.3 million fractures attributable to osteoporosis occur each year in people age 45 and older, and this condition is responsible for 50% of fractures occurring in women over age 50. Although all bones are affected, compression fractures of the vertebrae and traumatic fractures of the wrist and femoral neck are most common. Gradual asymptomatic vertebral compression may be detectable only on radiographic examination. Loss of body height and development of kyphosis may be the only signs of vertebral collapse. After hip fracture, most elderly patients fail to recover normal activity, and mortality within 1 year approaches 20%. Fractures in the elderly often lead to loss of mobility and independence, social alienation, fear of further falls and fractures, and depression.

Osteoporosis occurs when bone resorption outpaces bone formation.

Mechanisms underlying osteoporosis are complex and probably diverse. Bone constantly undergoes cycles of resorption and formation (remodeling) to maintain the concentration of calcium and phosphate in the extracellular fluid. When serum calcium concentration drops, parathyroid hormone secretion increases, and this hormone stimulates bone resorption by osteoclasts to restore serum calcium levels to normal. Bone mass declines with age and is influenced by sex, race, menopause, and body weight-for-height. Dietary intake of calcium and vitamin D as well as intestinal and renal function affect calcium and phosphate homeostasis. The risk of osteoporosis is highest in postmenopausal women. Asian or white race, underweight, dietary calcium deficiency, sedentary lifestyle, alcohol use, and cigarette smoking appear to be independent risk factors. The decline of vitamin D<sub>3</sub> level with aging results in calcium malabsorption, which, in turn, stimulates bone resorption. Estrogen deficiency exacerbates this problem by increasing the sensitivity of bone to resorbing agents. Women who become amenorrheic because of rigorous athletic exercise and dietary restriction or eating disorders are at risk of osteoporosis. The formation and resorption of bone are also influenced by external physical factors such as body weight and exercise. Immobilization and prolonged bed rest produce rapid bone loss, while exercise involving weight-bearing has been shown both to reduce bone loss and to increase bone mass. Osteoporosis is common in young adults with cystic fibrosis, particularly those treated with long-term corticosteroid therapy. The diagnosis of primary osteoporosis is established by documentation of reduced bone density after exclusion of known causes of excessive bone loss. Radiographs are insensitive indicators of bone loss, since bone density must be decreased by at least 20–30% before the reduction can be appreciated. Standard diagnostic procedures are determination of bone mineral density at the ultradistal radius and midshaft radius by single-photon absorptiometry, and at

the hip and lumbar spine by dual-energy x-ray absorptiometry (DEXA). A quantitative ultrasound procedure recently approved by the FDA is comparable to bone density measurements by DEXA in predicting fractures due to osteoporosis. The goal of therapy in osteoporosis is prevention of fractures in susceptible patients. The appropriate timing and proper use of agents such as calcium, vitamin D, estrogen, bisphosphonates, calcitonin, and raloxifene and the role of exercise have generated major research efforts and considerable controversy. Intake of adequate amounts of calcium and vitamin D, and continuing moderate weight-bearing exercise, are basic preventive measures for persons of all ages. Administration of estrogen at and after menopause does not simply halt the loss of bone, but actually increases bone mass. Hormone replacement with estrogen remains the most effective prevention and treatment for postmenopausal osteoporosis. It is believed to be most appropriate to start estrogen at the earliest sign of the menopause, since bone loss probably begins before the cessation of menses. Estrogen therapy must be continued through later life to maintain optimal bone density. There is no convincing evidence that initiating estrogen therapy in elderly women will prevent osteoporosis. The benefits of estrogen therapy must be weighed against the increased risk of endometrial hyperplasia and endometrial carcinoma (which can be offset by concomitant administration of progestogen) and possibly of carcinoma of the breast. The selective estrogen receptor modulator raloxifene has been approved for prevention of osteoporosis. It does not cause endometrial hyperplasia but is less effective than estrogen in conserving bone mass. The hormone calcitonin, administered by injection or nasal spray, inhibits bone resorption and has other effects on mineral metabolism. Bisphosphonates such as alendronate and etidronate, which bind to bone crystals, rendering them resistant to enzymatic hydrolysis and inhibiting the action of osteoclasts, have been shown to increase bone mineral density. Strategies to prevent falls are important in elderly patients. SEE ALSO estrogen replacement therapy, raloxifene.

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**hyperparathyroidism** (hī'per-par-ă-thī'royd-izm)

A condition due to an increase in the secretion of the parathyroids, causing elevated serum calcium, decreased serum phosphorus, and increased excretion of both calcium and phosphorus, calcium stones and sometimes generalized osteitis fibrosa cystica.

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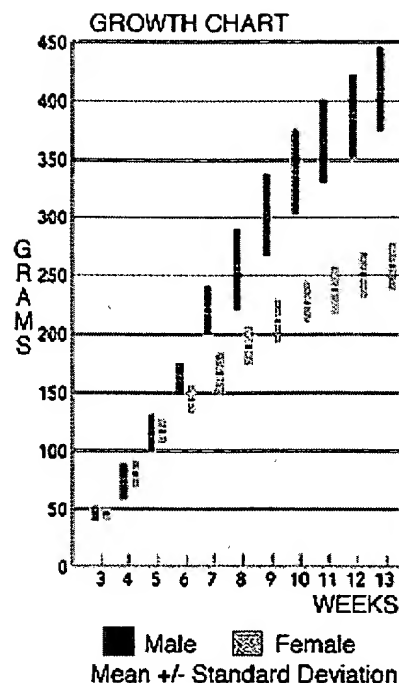
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**Order Model #:** SD

**Color:** Albino

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